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MCDONNELL BOEHNEN HULBERT @ BERGHOFF LLP
300 SOUTH WACKER DRIVE
SUITE 3100
CHICAGO, IL 60606

EXAMINER	
COLEMAN, BRENDA LIBBY	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,702	MARTIN ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *6-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 32-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/06; 1/3/07; & 1/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :1/23/2006; 1/3/2007; & 1/26/2007.

DETAILED ACTION

Claims 1-48 are pending in the application.

Election/Restrictions

1. Applicant's election of Group I in the reply filed on February 5, 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 6-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 5, 2010.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5 and 32-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for salt forms, does not reasonably provide enablement for solvates or polymorphs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The claim is drawn to solvates or polymorph. But the numerous examples presented all failed to produce a solvate or

polymorph. These cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. Hence, applicants must show that solvates or polymorphs can be made, or limit the claims accordingly.

4. Claims 1-5 and 32-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is the Wands factors, which are used to evaluate the enablement question. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the instant invention has claims which embrace substituted 1,2,3,6,7,8,9,10-octahydro-azepino[4,5-*b*]indoles. The scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active in vivo. The choice of a "prodrug" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which will be suitable for the instant invention.

The instant compounds of formula I wherein the pro-drugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare

the various compounds suggested by claims 1-5 and 32-45. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

5. Claims 46-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the instant invention has claims, which embrace substituted 1,2,3,6,7,8,9,10-octahydro-azepino[4,5-*b*]indole compounds.

HOW TO USE: Claims 46-48 are drawn to the compositions and method of treating, preventing, or ameliorating one or more symptoms of a disease or disorder, which is associated with Farnesoid X receptor activity. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the

effectiveness of the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims of the instant invention call for the treatment, prevention or ameliorating any and all diseases associated with Farnesoid X receptor. The scope of claim 47 includes diseases and/or conditions not even known at this time, which may be associated with Farnesoid X receptor activity. While the treatment of hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, lipodystrophy, atheroslerosis, atherosclerotic disease has been linked with Farnesoid X the art does not recognize use of such inhibitors as broad based drugs for treating all disorders instantly embraced.

It is difficult to treat many of the disorders claimed herein. Instant claim language embraces disorders not only for treatment but the **prevention**, which is not remotely enabled. It is presumed in the prevention of the diseases and/or disorders claimed herein there is a way of identifying those people who may develop a tolerance to opiate analgesia, etc. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders claimed herein.

Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of in vivo efficacy by those skilled in the art. See *In re Ruskin*, 148 USPQ 221; *Ex parte Jovanovics*, 211 USPQ 907; MPEP 2164.05(a).

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. *Genentech Inc. v. Novo Nordisk* 42 USPQ2d 1001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-5 and 32-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a. Claim 1 and claims dependent thereon recites the limitation "R^{33}, R^{34}" in the second line on page 3. There is insufficient antecedent basis for this limitation in the claim.

b. Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the period that appears at the end of the definition of R^4, R^5, R^6 and R^7.

c. Claim 1 and claims dependent thereon recites the limitation "R^{15}, R^{16}" in the 10^{th} line to the bottom of page 4. There is insufficient antecedent basis for this limitation in the claim.

d. Claim 1 and claims dependent thereon recites the limitation "R^{21}, R^{22}" in the last line on page 4. There is insufficient antecedent basis for this limitation in the claim.

e. Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the range R^1-R^{24} and R^{30}-R^{36}, which does not specify that which is embraced by the range.

f. Claim 1 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the moiety $-N^+(R^{77})_3$ in the definition of Q^1 and Q^2, which is an ion but there is no indication of the counterion.

g. Claims 34-42 and 44 are vague and indefinite in that it is not known what is meant by derivative" which implies more then what is positively recited.

h. Claim 34 and claims dependent thereon recites the limitation "R^{15}, R^{16}" in the 7th line from the bottom of page 18. There is insufficient antecedent basis for this limitation in the claim.

i. Claim 34 and claims dependent thereon recites the limitation "R^{21}, R^{22}" in the third line on page 19. There is insufficient antecedent basis for this limitation in the claim.

j. Claim 34 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the range R^1-R^{24}, which does not specify that which is embraced by the range.

k. Claim 34 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the moiety $-N^+(R^{77})_3$ in the definition of Q^1 and Q^2, which is an ion but there is no indication of the counterion.

l. Claim 42 recites the limitation "-C(O)OH" in the definition of R^1. There is insufficient antecedent basis for this limitation in the claim.

m. Claim 42 recites the limitation "-C(O)N(CH_3)(cyclopropyl)" in the definition of R^1. There is insufficient antecedent basis for this limitation in the claim.

n. Claim 45 is recites the limitation "1,2,3,4,5,6,7,8,9,10-decahydro-azepino[4,5-b]indole" in the nomenclature of the first species in claim 45. There is insufficient antecedent basis for this limitation in the claim.

o. Claim 46 and claims dependent thereon recites the limitation "R^{33}, R^{34}" in the first line on page 24. There is insufficient antecedent basis for this limitation in the claim.

p. Claim 46 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the period that appears at the end of the definition of R^4, R^5, R^6 and R^7.

q. Claim 46 and claims dependent thereon recites the limitation "R^{15}, R^{16}" in the 12th line from the bottom of page 25. There is insufficient antecedent basis for this limitation in the claim.

r. Claim 46 and claims dependent thereon recites the limitation "R^{21}, R^{22}" in the 3rd line from the bottom of page 25. There is insufficient antecedent basis for this limitation in the claim.

s. Claim 46 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the range R^1-R^{24} and R^{30}-R^{36}, which does not specify that which is embraced by the range.

t. Claim 46 and claims dependent thereon are vague and indefinite in that it is not known what is meant by the moiety $-N^{+}(R^{77})_3$ in the definition of Q^1 and Q^2, which is an ion but there is no indication of the counterion.

u. Claim 47 is vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by a farnesoid X receptor. It is unclear which diseases are associated with each of the farnesoid X receptors. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to

work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in cancer and CNS diseases, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation

shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claim Objections

7. Claims 3-5, 32 and 33 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be stated in the alternative. See MPEP § 608.01(n).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brenda L. Coleman/
Primary Examiner, Art Unit 1624